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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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*Ex parte* DAVID WALLACH, ANDREI KOVALENKO,
MARSHALL S. HORWITZ, and YONGAN LI

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Appeal 2010-006439
Application 10/761,370
Technology Center 1600

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Before TONI R. SCHEINER, LORA M. GREEN, and STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a molecule comprising an antibody specific for an RIP associated protein-2. The Patent Examiner rejected the claims on the ground of obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

## STATEMENT OF THE CASE

Claims 1 and 17-19, which are all the pending claims, are on appeal. Claim 1 is representative and reads as follows:

1. A molecule comprising an antibody specific for a RAP-2 (RIP associated protein-2) protein, which RAP-2 protein has the sequence of SEQ ID NO:4, or a fragment of said antibody, which fragment is capable of binding to RAP-2.

The Examiner rejected claims 1 and 17-19 under 35 U.S.C. § 103(a) as unpatentable over the Li[1] thesis[2] in view of the Li journal article[3] and Ellis.[4]

## OBVIOUSNESS

*The Issue*

The Examiner's position is that Yongan Li's 1996 PhD thesis described a protein designated FIP-2 that comprised multiple leucine zipper domains. (Ans. 4.) As described in the journal article, Li tagged FIP-2 with a T7 peptide, and used anti-T7 tag antibodies to study FIP-2 in cells. (*Id.*) The Examiner found that "[b]y reading Yongan [Li], one of skill in the art would have known that antibodies against Fip-2 could be used to study

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[1] Appellants suggest that although "the examiner and applicant have referred to the references as 'Yongan,'" they "should more properly be referred to as Li et al. or the Li thesis." (Reply Br. 6 n.1.)

[2] Yongan Li, *Identification and characterization of cellular proteins which interact with adenovirus E3-14.7KDA protein an antagonist of TNF-α* (1996) (Abstract).

[3] Yongan Li et al., *Interaction of an Adenovirus E3 14.7-Kilodalton Protein with a Novel Tumor Necrosis Factor Alpha-Inducible Cellular Protein Containing Leucine Zipper Domains*, 18 MOLECULAR AND CELLULAR BIOL. 1601-1610 (1998).

[4] Jonathan H. Ellis et al., *Engineered Anti-CD38 Monoclonal Antibodies for Immunotherapy of Multiple Myeloma*, 155 J. IMMUNOL. 925-937 (1995).

interaction between intracellular proteins involved in signaling and their co-localization inside the cell (p. 1603, column 2, p. 1606, column 1)." (*Id.*) Thus, the Examiner concluded that it would have been obvious to raise polyclonal antibodies against FIP-2. (*Id.* at 4-5.) Because Li taught that the C-terminus of FIP-2 was necessary for its interaction with the adenoviral protein Ad E3-14.7K, and taught the importance of the leucine zipper motif in the C-terminal portion of FIP-2 (*id.* at 4), the Examiner found that a person of ordinary skill in the art "would have been motivated to obtain monoclonal antibodies against these domains to study their role in Fip-2 function" (*id.* at 5.) The Examiner reasoned that anti-FIP-2 polyclonal antibodies directed against the leucine zipper and C-terminal domains of FIP-2 "must necessarily be specific for RAP-2," because "the specification teaches that the leucine zipper domain of Fip-2 is preserved in RAP-2 (encoded by SEQ ID NO: 4), wherein the leucine zipper domain is located in the C-terminal domain of RAP-2; the specification also teaches that the C-terminal amino acids are identical in Fip-2 and Rap-2 (see paragraphs 0019 and 0088; Fig. 3B)." (*Id.* at 5-6.)

Appellants present these arguments for reversal:

(1) assuming antibodies against FIP-2 would have been obvious, the majority of those antibodies would not have bound RAP-2, and to the extent there would have been any anti-RAP-2 antibodies within that genus, that subgenus of antibodies defined in claim 1 has the unexpected property of binding RAP-2, and would therefore have been unobvious (App. Br. 9-15);

(2) it is not prima facie obvious that any antibody that can be raised against FIP-2 will necessarily bind to RAP-2 (*id.* at 16-19);

(3) claims 17 and 18 are patentable in their own right as monoclonal antibodies would not have been obvious (*id.* at 19-21);

and

(4) interpreting claim 1 to include antibodies that bind FIP-2 is incorrect because an antibody "specific" for a RAP-2 protein "[a]t the very least . . . must have preferential binding to RAP-2," and "[t]he polyclonal antibodies that would be obtained when using FIP-2 as an immunogen, would not be 'specific for' RAP-2 as they would preferentially bind to FIP-2 and only incidentally bind to RAP-2 (if at all) because only a small percentage of those antibodies (if any) would have the property of binding to RAP-2." (Reply Br. 4.)

*Findings of Fact*

1. We adopt the Examiner's findings concerning the scope and content of the prior art.
2. We adopt the Examiner's findings concerning the scope and content of Appellants' Specification.
3. Appellants' Specification discloses:

> FIP-2 was found to have some homology to RAP-2, the protein of the present invention. The degree of overall similarity between RAP-2 and FIP-2 nevertheless is fairly low, as can be seen from the global alignment of the two amino acid sequences (Figure 3). The homology however becomes more significant in specific regions towards the C-terminus of the proteins, culminating in virtual identity of the 30 C-terminal amino acids. It is noteworthy that, besides the above mentioned C-terminal domain, the putative Leucine Zipper motif in FIP-2 is largely preserved in RAP-2 (except for an Ile to Ala substitution).
>
> (Spec. ¶ [0019].)

4. The Specification's Brief Description of Figure 3 reads:

> Figure 3 A (/1, /2) shows the deduced amino acid sequences of the human (20.4 full and *Human* shrt) and murine (NEMO full and *Mouse* part) splice variants of RAP-2 and B (/1, /2) shows the published sequence of FIP-2 aligned using the software package available at the BCM Search Launcher (Baylor College of Medicine, Houston, TX). Homologous amino acids are boxed, identical amino acids are gray-shaded. Asterisks in (B) denote a putative leucine-zipper (LZ)-like motif in FIP-2.

(*Id.* at [0088].)

6. Figure 3(B)'s RAP-2 and FIP-2 alignment displays the C-terminal region correspondence in Fig. 3(B)2. (*Id.*)

*Principles of Law*

"[I]t is not necessary in order to establish a *prima facie* case of obviousness ... that there be a suggestion in or expectation from *the prior art* that the claimed compound or composition will have the same or a similar utility *as one newly discovered by applicant.*" *In re Dillon*, 919 F.2d 688, 693 (Fed. Cir. 1990) (en banc) (emphasis in original). "Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). "Obviousness does not require absolute predictability. Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness." *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (citations omitted).

*Analysis*

The Examiner found that Li's disclosure of the importance of FIP-2's C-terminus and leucine zipper domains suggested that antibodies targeting those C-terminus and leucine zipper domains would have been useful, and

thereby suggested such antibodies. We agree that the evidence supports that finding and have adopted it. (FF 1.) The Examiner also found that polyclonal anti-FIP-2 antibodies would necessarily include antibodies binding RAP-2. We agree that the evidence of substantial structural similarity between the C-terminal regions of the two proteins is prima facie sufficient evidence that polyclonal antibodies against FIP-2 would necessarily include antibodies that cross react with RAP-2.

Appellants' argument (4) concerns claim interpretation, and we therefore will address Appellants' arguments (1) and (4) together, followed by arguments (2) and (3).

Issues (1) and (4)

For purposes of their first argument, Appellants concede that the Examiner established the obviousness of a composition of polyclonal antibodies against FIP-2, but contend that "the subgenus (or subset) of the antibodies encompassed by claim 1 possess a property that would have been totally unexpected from the genus (or set) of antibodies allegedly made obvious." (App. Br. 9.) According to Appellants, "[t]he present claims are *effectively* species or subgenus claims directed to that relatively small subset (if it exists at all) of the prior art genus of anti-Fip-2 antibodies that will also bind to RAP-2." (*Id.* at 10, emphasis added.) In other words, because FIP-2 has large areas not homologous to RAP-2, it would not be expected that every antibody against FIP-2 will necessarily bind RAP-2. "To the extent that there are any anti-RAP-2 antibodies within this genus, they represent only a species or subgenus thereof," but that subgenus would not have been obvious even if the genus that encompasses them would have been obvious. (*Id.*)

The Examiner did not object to Appellants' technical explanation, but disagreed that the claims are effectively limited to a subgenus. Claim 1 does not define a *purified* subgenus as the Examiner interpreted the claim: "the claims do not require that the antibodies specific for RAP-2 (i.e., the subgenus) be isolated from the polyclonal preparation (i.e., the genus)." (Ans. 15.) That is, the claimed "antibody" is not defined at any level of purity or isolation from other antibodies, and the claim covers an unpurified RAP-2 binding antibody as it exists in the proposed polyclonal anti-FIP-2 mixture. (*Id.*; see also, Adv. Action, mailed Apr. 7, 2010.)

Appellants contend that the Examiner's interpretation "read[s] out" the "specific for" language of the claims. (Reply Br. 2-3.) We disagree. A claim reciting "a compound" does not distinguish the compound over trace amounts of the compound in prior art compositions of other materials. *See, e.g., SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1344 (Fed. Cir. 2005) (trace amounts contaminating other preparations anticipated a claim reading only "crystalline paroxetine hydrochloride hemihydrate"). Here, claim 1 recites only "an antibody" and does not distinguish the claimed antibody from RAP-2 antibody present in the suggested composition of polyclonal antibodies, even if most of the antibodies in that composition would not bind RAP-2 and would not be specific for RAP-2. We therefore agree with the Examiner that claim 1 does not effectively distinguish its subject from the obvious composition. Put another way, the prior art need not suggest how to make the antibody in isolated form; it need only suggest how to make the antibody in any form encompassed by claim 1. *Compare, Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d

1373, 1381 (Fed. Cir. 2003) (applying this principle in an anticipation context).

We thus also agree with the Examiner's explanations that (1) because claim 1 does not define a selection invention, MPEP § 2144.08 is not persuasive (Ans. 15-16), and (2) binding RAP-2 is an inherent, or latent, property of at least some antibodies in the obvious composition of anti-FIP-2 antibodies (*id.* at 16). *See Baxter Travenol Labs.*, 952 F.2d at 392. These facts also distinguish this case from *In re May*, 574 F.2d 1082 (CCPA 1978), which Appellants cited at oral argument. (Transcript at 6.)

The antibodies in the claims are defined as "specific" for a RAP-2 protein, and the Reply Brief references Spec. ¶¶ [0166] and [0168], which both indicate that the RAP-2 protein may be used to produce or generate "**specific** antibodies thereto" or "antibodies **specific** to RAP-2 proteins," respectively. (Reply Br. 3-4.) According to Appellants, "[a]t the very least, this means that the antibodies, whether polyclonal or monoclonal, must have preferential binding to RAP-2," but antibodies raised against FIP-2 would not be specific for RAP-2 as they would "only incidentally bind to RAP-2 (if at all)." (*Id.* at 4.) No definition of "specific" was placed in evidence by either side in this dispute. No standard for "preferential" vis-à-vis "incidental" binding, as a person of ordinary skill in the art would use these terms, has been placed in evidence. It is not established that a person of ordinary skill in the art, evaluating antibody binding to FIP-2 or to RAP-2 via a common epitope, could actually determine which protein had been used as the antigen. The Examiner found that FIP-2 and RAP-2 have epitopes in common, and that the shared epitopes were sufficient to elicit immune responses. (Ans. 17-18.)

The meaning of "specific" was also explored at the oral hearing, July 21, 2011:

> Q: Mr. Browdy, does it make sense to say that an antibody that binds to two different proteins is specific for either one of them?
> A: I think that the answer is yes. I could foresee a situation where an antibody raised against a polypeptide of one protein that binds to that identical region two different proteins can be said to be specific for both of them. I don't think that the word specific necessarily means that it'll bind to one protein and only one protein in the world. I'll leave it at that.
> Q: So you're not saying that your claim excludes antibodies that would also bind with the prior art protein?
> A: Absolutely not. My claims are drawn to any antibody that binds to RAP2.
> Q: So why isn't that --
> A: They all have the common property. All my claimed antibodies have the common property of binding to RAP2. Now, if some of those antibodies -- not all of them -- if some of those antibodies also bind to FIP2, I don't care. They may have other properties I don't know about.
> Q: I guess my question is I know we're not talking about anticipation here. We have an obviousness rejection. But I guess my question is why wouldn't those antibodies -- let's assume for the moment there is a reason for someone to make antibodies to those common residues of the prior art protein or to make antibodies to that entire prior art protein in some of those antibodies --
> A: May or may not bind to RAP2.
> Q: -- cross react to the two proteins. Why wouldn't those antibodies meet the requirements of your claim since your claim doesn't exclude things that bind other proteins besides RAP2?
> A: I understand. The answer is that if such antibodies existed, and going back to the first part of my argument, we don't know that the overlapping portion is on the outside of the protein. We don't know that you could raise antibodies against that portion that will necessarily bind to RAP2. We don't know if that portion is on the interior or exterior of the RAP2 protein. We don't know that if you raise antibodies against that area, or if you raise antibodies to the whole thing there's going to be any antibodies that necessarily bind to RAP2.

(Transcript at 3-4.) After weighing the arguments, we think the Examiner has the better position on the meaning of "specific."

We have considered Appellants' argument that the common epitopes, e.g., the leucine zipper motif, might be concealed on FIP-2. The Examiner initially directed attention to Li's disclosure that FIP-2's two leucine zipper domains may be involved in signaling. (Ans. 4, citing Li at 1608.) The Examiner was unpersuaded by Appellants' contention that some of the epitopes "might be folded within the protein," because it was unsupported by evidence. (Ans. 18.) Because the prior art disclosed a potential signaling role for the leucine zipper domains, we agree with the Examiner that evidence of concealment, not hypothetical argument, is needed.

Issue (2)

The Examiner relied on the Inventors' description of similarity between FIP-2 and RAP-2 as the basis for finding that anti-FIP-2 antibodies recognizing certain domains of FIP-2 would necessarily be specific for RAP-2. (Ans. 5-6, citing Spec. ¶¶ [0019] and [0088] and Figure 3(B).) According to the Specification at ¶ [0019], although overall similarity between the two proteins is low, the homology becomes more significant in specific regions towards the C-terminus of the proteins, culminating in "virtual identity" of the 30 C-terminal amino acids, and the leucine zipper motif is "largely preserved in RAP-2 except for an Ile to Ala substitution." (FF 3.)

The Appeal Brief suggests that "it is not necessary to rely on the characterizations in paragraphs [0019] and [0021], as done by the examiner, as one can actually see what is identical and what is preserved in Figure 3B."

(App. Br. 16.) The Brief then records its own observations of Figure 3B, seeming to suggest that the Inventors' descriptions of "virtual identity" and "largely preserved" may be discounted in view of the contrary opinion offered in the Brief. We treat this as attorney argument, not evidence, and give it little weight against the Inventors' descriptions. We similarly give little weight to the Brief's speculations about the possibility that features of the protein are not exposed on the surface, or the possibility that even if an antibody were raised to a portion of FIP-2, the antibody might not bind to RAP-2, because there is no evidence showing these are reasonable speculations.

Claim 19 has not been argued separately and therefore falls with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

Issue (3), Claims 17 and 18

Appellants contend that there is no guarantee that in any given round of hybridoma production, the anti-FIP-2 antibodies found would necessarily be directed to that portion of FIP-2 that happens to overlap with RAP-2. (App. Br. 19.) That may be so, but it is the nature of the art that hybridomas are produced and then screened for the desired antibody. *See, e.g.*, the summary of the screening technique in *In re Wands*, 858 F.2d 731, 737-738 (1988). The test for obviousness is that there be a reasonable expectation of success, not that success be guaranteed in a particular round of screening. There is no evidence, on this record, that one round was the standard by which persons of ordinary skill would judge the likelihood of success. *See Merck & Co.*, 800 F.2d at 1097.

Appellants also contend that "[o]ne cannot simply assume that monoclonal antibodies can be raised against every possible region of a

protein," and "[s]ome regions may be folded within the protein or be obscured." (*Id.* at 20.) In the abstract, this general point might be correct. In this case, however, Li described the C-terminal portion of FIP-2 as interacting with E3-14.7K (Li at 1603), which casts doubt on the likelihood that it is obscured. The Examiner also responded that even if some epitopes were obscured, one would have expected reasonable success in obtaining monoclonals against the exposed epitopes (Ans. 18), and Appellants do not dispute that response in their Reply.

## CONCLUSION

Considering all the evidence of record, we conclude that the Examiner has produced sufficient evidence to support the case for obviousness. Appellants' arguments are similar to arguments in the *Wiseman* case, which the court did not accept: "[Appellants] are, in effect, arguing that a structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable to them because it also possesses an Inherent, but hitherto unknown, function which they claim to have discovered. This is not the law. A patent on such a structure would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art." *In re Wiseman*, 596 F.2d 1019, 1023 (CCPA 1979); *see also In re Kubin*, 561 F.3d 1351, 1357-58 (Fed. Cir. 2009).

## SUMMARY

We affirm the rejection of claims 1 and 17-19 under 35 U.S.C. § 103(a) as unpatentable over the Li thesis in view of the Li journal article and Ellis.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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